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(54) Title: BIPIPERIDINYL-DERIVATIVES AND THEIR USE AS CHEMOKINE RECEPTORS INHIBITORS

(57) Abstract: Piperidine derivatives of formula (I) as disclosed in the specification have interesting pharmaceutical properties e.g. as CCR5 inhibitors.

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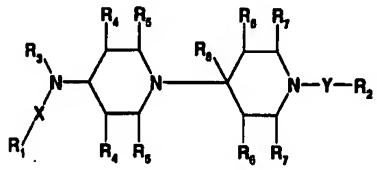
BIPIPERIDINYL-DERIVATIVES AND THEIR USE AS CHEMOKINE RECEPTORS INHIBITORS

The present invention relates to piperidine derivatives, process for their production, their uses and pharmaceutical compositions containing them.

More particularly, the present invention provides a compound of formula I



I

wherein

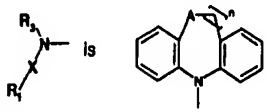
X is a direct bond; $-CH_2-$; $-CH_2-CH_2-$; $-CHR_9-$; $-C(O)-$; $-O-$; $-NH-$ or NR_9;

R_1 is optionally R_{10} and/or R_{11}-substituted phenyl; optionally R_{10} and/or R_{11}-substituted heteroaryl; optionally R_{10} and/or R_{11}-substituted heteroaryl N-oxide; or optionally R_{10} and/or R_{11}-substituted naphthyl;

R_2 has one of the significances given for R_1; or is optionally R_{10} and/or R_{11}-substituted fluorenyl; optionally R_{10}-substituted C_1-C_8 alkyl; optionally R_{10}-substituted C_2-C_8 alkenyl; optionally R_{10}-substituted C_3-C_8 cycloalkyl; optionally R_{10}-substituted adamantyl; or optionally R_{10}-substituted C_4-C_8 cycloalkenyl;

R_3 has one of the significances given for R_1; or is optionally R_{10} and/or R_{11}-substituted fluorenyl; R_{10}-substituted C_1-C_8 alkyl; optionally R_{10}-substituted C_2-C_8 alkenyl; optionally R_{10}-substituted C_3-C_8 cycloalkyl; optionally R_{10}-substituted adamantyl; or optionally R_{10}-substituted C_4-C_8 cycloalkenyl;

or



wherein A is $-CH_2-$, $-NH-$, $-NR_9-$, $-S-$, $-SO-$, SO_2- or $-O-$, n is 0, 1 or 2, and the aromatic rings are each, independently optionally R_{10}-substituted;

each of R4, independently, has one of the significances of R_5; or is CN; OH; OR_9; F; Cl; Br; or I;

each of R_5, independently, is H; C_1-C_6 alkyl; C_1-C_6 hydroxyalkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; phenyl; benzyl; or heteroaryl;

each of R_6, independently, has one of the significances given for R_4;

each of R_7, independently, has one of the significances given for R_5;

R_8 is H; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl; benzyl; CN; CH_2NH_2; CH_2NHR_9; $CH_2NR_9R_9$; $CH_2NHC(O)R_9$; $CH_2NR_9C(O)R_9$; $CH_2NHC(O)NHR_9$; $CH_2NR_9C(O)NHR_9$; $CH_2NR_9C(O)NR_9R_9$; $CH_2NHC(O)OR_9$; $CH_2NR_9C(O)OR_9$; $CH_2NHSO_2R_9$; $CH_2N(SO_2R_9)_2$; or $CH_2NR_9SO_2R_9$;

each R_9, independently, is C_1-C_6 alkyl; C_3-C_6 cycloalkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl; benzyl; heteroaryl; or CF_3;

R_{10} represents 1 to 4 substituents independently selected from C_1-C_6 alkyl; C_1-C_6 hydroxyalkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; C_3-C_6 cycloalkyl; C_2-C_6 alkenyl; C_3-C_6 cycloalkenyl; C_2-C_6 alkynyl; phenyl; heteroaryl; heteroaryl N-oxide ; F; Cl; Br; I; OH; OR_9; $CONH_2$; $CONHR_9$; $CONR_9R_9$;$OC(O)R_9$; $OC(O)OR_9$; $OC(O)NHR_9$; $OC(O)NR_9R_9$; OSO_2R_9; COOH; $COOR_9$; CF_3; CHF_2; CH_2F; CN; NO_2; NH_2; NHR_9; NR_9R_9; $NHC(O)R_9$; $NR_9C(O)R_9$; $NHC(O)NHR_9$; $NHC(O)NH_2$; $NR_9C(O)NHR_9$; $NR_9C(O)NR_9R_9$; $NHC(O)OR_9$; $NR_9C(O)OR_9$; $NHSO_2R_9$; $N(SO_2R_9)_2$; $NR_9SO_2R_9$; SR_9; $S(O)R_9$; SO_2R_9; $Si(CH_3)_3$ and $B(OC(CH_3)_2)_2$;

R_{11} represents two adjacent substituents which form an annulated 4-7 membered nonaromatic ring optionally containing up to two heteroatoms selected independently from N, O and S; and

Y is a direct bond; -C(O)-; $-C(O)CH_2-$; -S(O)-; $-S(O_2)-$; -C(S)-; $-CH_2-$; $-C(-CH_2-CH_2-)-$; $-CH(R_4)-$ or $-C(R_8)_2-$,

in free form or in salt form.

Any alkyl, alkenyl or alkynyl may be linear or branched. Halogeno is F, Cl, Br or I.

By heteroaryl is meant an aromatic ring system comprising mono-, bi- or tricyclic systems which contains up to 4 heteroatoms independently selected from N, O and S, such as for example furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, tetrazinyl, indolyl, benzothiophenyl, benzofuranyl, benzimidazolyl, indazolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl or naphthyridinyl.

Preferred annulated 4-7membered non-aromatic ring as represented by R_{11} is annulated 5 or 6 membered non aromatic ring optionally containing 1 or 2 oxygen and include e.g.

$-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$, attached to 2 adjacent carbon atoms.

The compounds of formula I may exist in free form or in salt form, e.g. addition salts with e.g. organic or inorganic acids, for example, hydrochloric acid, acetic acid when R_1, R_2, and /or R_3 comprises an optionally substituted amino group or a heterocyclic residue which can form addition salts. When the compounds of formula I have one or more asymmetric centers in the molecule, e.g. when a piperidine ring is substituted, the present invention is to be understood as embracing the various optical isomers, as well as racemates, diastereoisomers and mixtures thereof.

In the compounds of formula I, the following significances are preferred individually or in any sub-combination:

1. R_1 is optionally R_{10}-substituted phenyl; optionally R_{10}-substituted heteroaryl; or optionally R_{11}-substituted phenyl,

2. R_2 is optionally R_{10}-substituted phenyl; optionally R_{10}-substituted heteroaryl; optionally R_{10}-substituted heteroaryl N-oxide; or optionally R_{10}-substituted naphthyl.

3. R_3 is optionally R_{10}-substituted phenyl; optionally R_{10}-substituted heteroaryl; or optionally R_{10}-substituted naphthyl.

4. Each of R_4, R_5, R_6 or R_7, independently, is H; C_1-C_6 alkyl; or benzyl.

5. R_8 is H; C_1-C_6 alkyl; or C_2-C_6 alkenyl.

6. R_9 is C_1-C_6 alkyl; C_3-C_6 cycloalkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl; benzyl; heteroaryl; or CF_3.

7. R_{10} represents 1 to 3 substituents independently selected from C_1-C_6 alkyl; C_1-C_6 hydroxyalkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; C_3-C_6 cycloalkyl; C_2-C_6 alkenyl; C_3-C_6 cycloalkenyl; C_2-C_6 alkynyl; phenyl; heteroaryl; heteroaryl N-oxide; F; Cl; Br; I; OH; OR_9; $CONH_2$; $CONHR_9$; $CONR_9R_9$; $OC(O)R_9$; $OC(O)OR_9$; $OC(O)NHR_9$; $OC(O)NR_9R_9$; OSO_2R_9; COOH; $COOR_9$; CF_3; CHF_2; CH_2F; CN; NO_2; NH_2; NHR_9; NR_9R_9; $NHC(O)R_9$; $NR_9C(O)R_9$; $NHC(O)NHR_9$; $NHC(O)NH_2$; $NR_9C(O)NHR_9$; $NR_9C(O)NR_9R_9$; $NHC(O)OR_9$; $NR_9C(O)OR_9$; $NHSO_2R_9$; $N(SO_2R_9)_2$; $NR_9SO_2R_9$; SR_9; $S(O)R_9$; SO_2R_9 and $Si(CH_3)_3$.

8. R_{11} represents $-O-CH_2-O-$ attached on 2 adjacent carbon atoms.

9. X is a direct bond or $-CH_2-$.

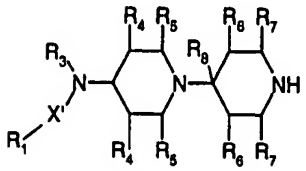
10. Y is -C(O)-.

In the preferred compounds of formula I, R_{10} may represent 1-3 substituents selected from from C_{1-6}alkyl; phenyl; heteroaryl; heteroaryl N-oxide; F; Cl; Br; I; OH; OR_9; $CONH_2$; $CONHR_9$; $CONR_9R_9$; COOH; $COOR_9$; CF_3; CHF_2; CH_2F; NH_2; NHR_9; NR_9R_9; $NHC(O)R_9$; $NR_9C(O)R_9$; $NHC(O)NHR_9$; $NHC(O)NH_2$; $NR_9C(O)NHR_9$; $NR_9C(O)NR_9R_9$; $NHC(O)OR_9$ and $NR_9C(O)OR_9$.

R_9 is preferably C_1-C_6 alkyl; C_3-C_6 cycloalkyl; phenyl; benzyl; or heteroaryl; more preferably C_1-C_6 alkyl.

The present invention also includes a process for the preparation of a compound of formula I which process comprises

a) for the preparation of a compound of formula I wherein X is a direct bond, $-CH_2-$, $-CH_2-CH_2-$ or $-CHR_9-$ and Y is -CO-, $-C(O)CH_2-$, -S(O)- or $-S(O_2)-$, amidating a compound of formula II



II

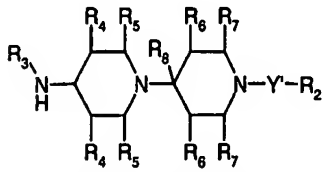
wherein R_1 and R_3 to R_8 are as indicated above and X' is a direct bond, $-CH_2-$, $-CH_2-CH_2-$ or $-CHR_9-$ with a compound of formula III

$$R_2\text{-}Y'\text{-}A' \qquad III$$

wherein R_2 is as defined above, Y' is -CO-, $-C(O)CH_2-$, -S(O)- or $-S(O_2)-$ and A' is a leaving group, e.g. Cl or Br,

b) for the preparation of a compound of formula I wherein X is a direct bond and Y is $-CH_2-$, submitting a compound of formula II as defined above wherein X' is a direct bond, to a reductive amination; or

c) for the preparation of a compound of formula I wherein X is CH_2-, $-CH_2-CH_2-$ or $-CHR_9-$ and Y is -CO-, $-C(O)CH_2-$, -S(O)- or $-S(O_2)-$, reacting a compound of formula IV



IV

wherein R_2 to R_8 and Y' are as defined above, with a compound of formula V

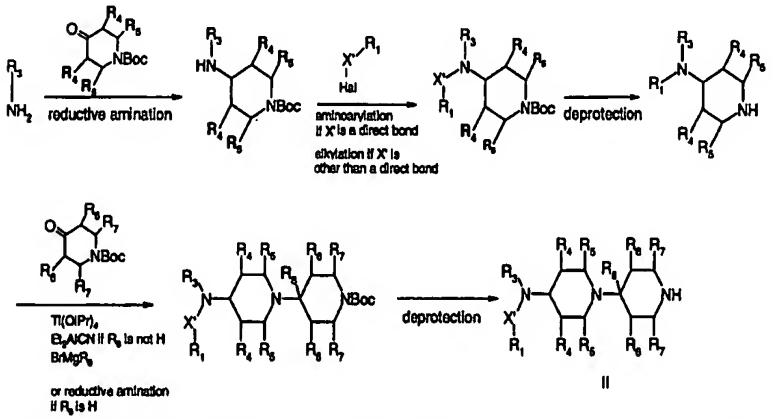
$$R_1\text{—}X''\text{—}Hal \qquad V$$

wherein R_1 is as defined above and X'' is CH_2- or $-CHR_9-$;

and, where required, converting the resulting compound of formula I obtained in free form into the desired salt form, or vice versa.

The reaction steps a), b) or c) may be performed in accordance with methods known in the art or as disclosed in the Examples below. When R_9 comprises a group which should not participate in the reaction, this group may be protected in accordance with methods known in the art.

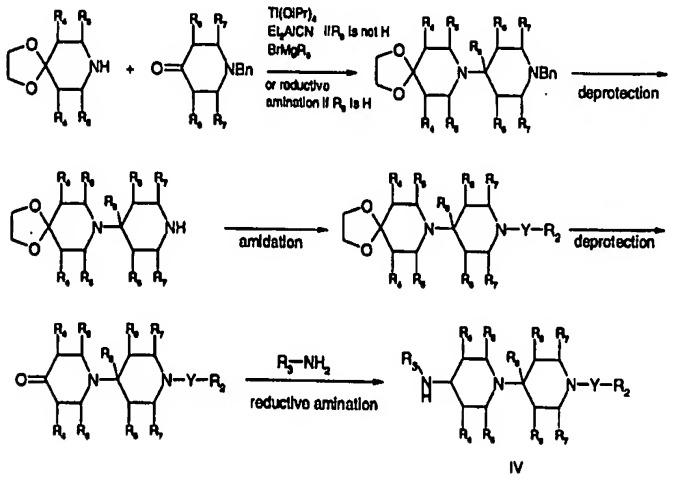
Compounds of formula II, used as starting material may be prepared as follows:



II

wherein X' and R_1 to R_8 are as defined above and Hal is Cl, Br or I. In above formulae, Boc is a protecting group which means tert.-butyloxycarbonyl. This protecting group may be replaced in above reaction scheme by any amino protecting group, e.g. as disclosed in "Protective Groups in Organic Synthesis" by T. W. Greene, J.Wiley & Sons NY, 2nd ed., Chapter 7, 1991 and references therein, e.g. benzyloxycarbonyl or 9-fluorenylmethoxy carbonyl.

Compounds of formula IV, used as starting material, may be prepared as follows:



IV

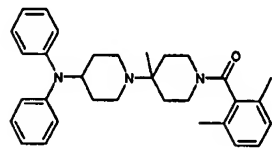
wherein R_2 to R_8 and Y are as defined above and Bn is benzyl.
Above reactions may be carried out in accordance with methods known in the art or as disclosed hereafter.

Insofar as the production of the starting materials is not particularly described, the compounds are known or may be prepared analogously to methods known in the art or as described hereafter.

The following Examples are illustrative of the invention, without limitation. Following abbreviations are used:

Bn	= Benzyl
Boc	= tert.-Butyloxycarbonyl
DMF	= Dimethylformamide
DMSO	= Dimethylsufoxide
BINAP	= 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
THF	= Tetrahydrofuran
TFA	= Trifluoroacetic acid
RT	= Room temperature

Example 1: (2,6-Dimethyl-phenyl)-(4-diphenylamino-4'-methyl-[1,4']bipiperidinyl-1'-yl)-methanone



A mixture of (4'-Methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine (0.25 g, 0.71 mmol), 2,6-dimethylbenzoic acid (0.32 g, 2.13 mmol), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (0.57 g, 1.5 mmol), $EtN(i\text{-}Pr)_2$ (0.6 ml) and DMF (5 ml) is stirred for 16 h at 20°C. The mixture is diluted with t-butyl methylether (25 ml), washed with 2N NaOH (25 ml) and brine (25 ml) and dried with sodium sulfate. The solvent is removed and the residue purified by chromatography (SiO_2, t-butyl methylether/cyclohexane 1:4→1:0). The title compound is isolated as a colorless solid. MS/ESI 482 $(M+H)^+$;
^{1}H NMR (400 MHz, DMSO) δ= 0.89 (3 H, s), 1.14-1.25 (3 H, m), 1.39 (1 H, m), 1.59 (1 H, m), 1.75 (1 H, m), 1.83-1.95 (2 H, m), 2.01 (3 H, s), 2.13 (3 H, s), 2.11-2.24 (2 H, m), 2.85 (2 H, m), 2.95 (1 H, m), 3.01 (1 H, m), 3.35 (1 H, m), 3.70-3.83 (2 H, m), 6.77 (4 H, m), 6.92-7.05 (4 H, m), 7.12 (1 H, m), 7.28 (4 H, m).

(4'-Methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine, used as starting material may be prepared as follows:

a) A mixture of phenyl-piperidin-4-yl-amine (4.14 g; 15.0 mmol), iodobenzene (3.06 g; 15.0 mmol), $Pd(OAc)_2$ (0.14 g; 0.63 mmol); BINAP (0.43 g; 0.69 mmol), t-BuOK (17.5 ml of 1M solution in THF) in toluene (20 ml) is heated at 110°C for 5 h. The mixture is diluted with ethyl acetate, extracted with sodium hydrogencarbonate and brine and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (SiO_2, *t*-butyl methylether /cyclohexane 1:9→1:1). 4-Diphenylamino-piperidine-1-carboxylic acid tert-butyl ester is isolated as a yellow solid. MS/ESI 353 $(M+H)^+$

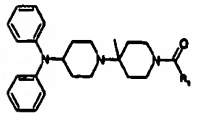
b) A mixture of TFA (5 ml), methylene chloride (5 ml) water (0.25 ml) and 4-diphenylamino-piperidine-1-carboxylic acid tert-butyl ester (1.5 g; 4.2 mmol) is stirred for 2 h at 20°C. Sodium hydroxide (4N) is added and the mixture extracted with ethyl acetate. The organic

phase is dried with sodium sulfate and the solvent removed. Diphenyl-piperidin-4-yl-amine is isolated as a colorless oil. MS/ESI 253 $(M+H)^+$

c) A suspension of diphenyl-piperidin-4-yl-amine (1.26 g, 5.00 mmol), 1-(tert-butyl oxycarbonyl)-4-piperidone (1.00 g, 5.00 mmol), and titanium(IV) isopropoxide (1.42 g, 5.00 mmol) in 1,2-dichloroethane (25 ml) is stirred for 1 h at 80°C and then for 16 h at 20°C. Diethylaluminum cyanide (10 ml 1M solution in toluene) is added and the mixture stirred for additional 24 h. The solvent is removed and the crude material dissolved in tetrahydrofuran (25 ml). Methylmagnesium bromide (8.7 ml 3M solution in ether) is added dropwise and the mixture stirred for 3 h at 20°C. Ammonium chloride (10 % solution, 50 ml) and ethyl acetate (50 ml) are added, the organic phase washed with ammonium chloride (10 % solution, 50 ml) and sodium hydrogencarbonate (10 % solution, 50 ml), dried with sodium sulfate and the solvent removed. The residue is subjected to chromatography (SiO_2, ethyl acetate/cyclohexane 1:9→1:1). 4-Diphenylamino-4'-methyl-[1,4']bipiperidinyl-1'-carboxylic acid tert.-butyl ester is isolated as a colorless solid MS/ESI 450 $(M+H)^+$.

d) A mixture of trifluoroacetic acid (2 ml) and water (0.1 ml) is added dropwise to a solution of compound a) above (0.81 g, 1.80 mmol) in methylene chloride (5 ml) and the mixture stirred for 3 h at 20°C. Sodium hydrogencarbonate (10% solution, 10 ml) and ethyl acetate (20ml) are added and the organic phase dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (RP-18, methanol/H_2O 1:3→0:1). The title compound is isolated as a colorless oil. MS/ESI 350 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) □= 0.88 (3 H, s), 1.35 (4 H, m), 1.60 (4 H, m), 1.93 (2 H, m), 2.15 (2 H, m), 2.58 (2 H, m), 2.87 (2 H, m), 2.96 (2 H, m), 3.76 (1 H, m), 6.78 (4 H, m), 6.94 (2 H, m), 7.22 (4 H, m).

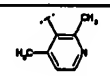
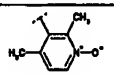
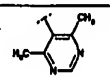
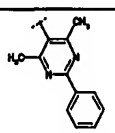
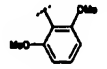
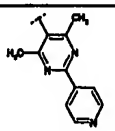
By following the procedure of Example 1 and using as starting material (4'-methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine, the compounds of formula X_1

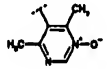
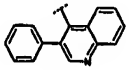


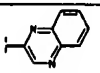
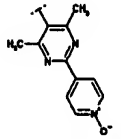
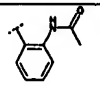
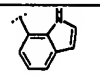
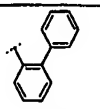
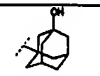
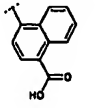
X_1

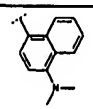
wherein R_2 has the significances as given in Table 1, may be prepared.

Table 1

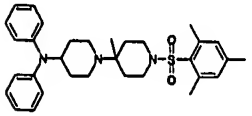
Example	R_2	MS/ESI $(M+H)^+$
2		483
3		499
4		460
5		454
6		470
7		522
8		468
9		484
10		560
11		514
12		561
13		488

14		523
15		504
16		500
17		506
18		539
19		498
20		525
21		488
22		506
23		505
24		581
25		535
26		505

27		506
28		521
29		505
30		505
31		518
32		577
33		511
34		493
35		493
36		530
37		528
38		548

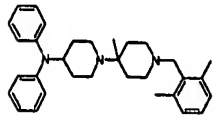
39		547
40		519

Example 41: **[4'-Methyl-1'-(2,4,6-trimethyl-benzenesulfonyl)-[1,4']bipiperidinyl-4-yl]-diphenyl-amine**



A mixture of (4'-methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine (70 mg, 0.20 mmol) and 2,4,6-trimethyl-benzenesulfonyl chloride (65 mg, 0.30 mmol) and diisopropyl ethylamine (0.50 ml) in methylene chloride (3 ml) is stirred for 4h at RT. The mixture is diluted with ethyl acetate, extracted with sodium hydrogencarbonate (10 % solution) and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (SiO_2, t-butyl methylether/cyclohexane 1:9→1:0). The title compound is isolated as a colorless solid. MS/ESI 532 $(M+H)^+$

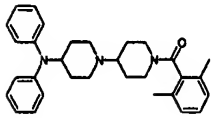
Example 42: **[1'-(2,6-Dimethyl-benzyl)-4'-methyl-[1,4']bipiperidinyl-4-yl]-diphenyl-amine**



A mixture of (4'-Methyl-[1,4']bipiperidinyl-4-yl)-diphenyl-amine (70 mg, 0.20 mmol) and 2,6-dimethyl-benzaldehyde (34 mg, 0.25 mmol) and $Na(OAc)_3BH$ (53 mg, 0.25 mmol) in 1,2-dichloroethane (10 ml) is stirred at RT for 16 h. The mixture is diluted with ethyl acetate, extracted with sodium hydrogencarbonate (10 % solution) and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (SiO_2, tert-butyl

methylether/methanol 1:0→10:1). The title compound is isolated as a colorless solid. MS/ESI 468 $(M+H)^+$

Example 43: **(2,6-Dimethyl-phenyl)-(4-diphenylamino-[1,4']bipiperidinyl-1'-yl)-methanone**



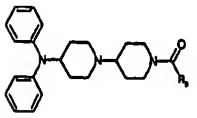
A mixture of TFA salt of [1,4']bipiperidinyl-4-yl-diphenyl-amine (77 mg, 0.23 mmol), 2,6-dimethylbenzoic acid (100 mg, 0.67 mmol), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (254 mg, 0.67 mmol), $EtN(i\text{-}Pr)_2$ (2 ml) and DMF (3 ml) is stirred for 5 h at RT. The mixture is diluted with tert-butyl methylether (10 ml), washed with 2N NaOH and brine and dried with sodium sulfate. The solvent is removed and the residue purified by chromatography (SiO_2, *t*-butyl methylether/cyclohexane 1:1→ethyl acetate→ethyl acetate/H_2O 98:2). The title compound is isolated as a colorless solid. MS/ESI 468 $(M+H)^+$

[1,4'] Bipiperidinyl-4-yl-diphenylamine, used as starting materials, may be prepared as follows:

a) A mixture of diphenyl-piperidin-4-yl-amine (1.06 g; 4.2 mmol), 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (1.0 g; 5.0 mmol), AcOH (0.62 g; 10.3 mmol) and $Na(OAc)_3BH$ (1.0 g; 4.7 mmol) in 1,2-dichloroethane (15 ml) is stirred for 4h at 65°C. The mixture is diluted with *t*-butyl methylether, extracted with 1N NaOH and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (SiO_2, *t*-butyl methylether/cyclohexane 1:9→1:0). 4-Diphenylamino-[1,4']bipiperidinyl-1'-carboxylic acid tert-butyl ester is isolated as a colorless solid. MS/ESI 436 $(M+H)^+$

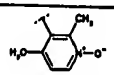
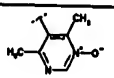
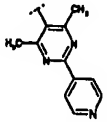
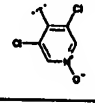
b) A mixture of 4-Diphenylamino-[1,4']bipiperidinyl-1'-carboxylic acid tert-butyl ester (1.06 g; 2.4 mmol), TFA (2.5 ml), H_2O (0.25 ml) and methylene chloride (5 ml) is stirred at RT for 4 h. The mixture is added dropwise to ether and the precipitate formed is filtered off. The TFA salt of [1,4']bipiperidinyl-4-yl-diphenyl-amine is isolated as a colorless solid. MS/ESI 336 $(M+H)^+$

By following the procedure of Example 2 above and using as starting materials [1,4']bipiperidinyl-4-yl-diphenyl-amine the compounds of formula X_2

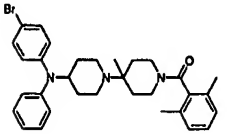


wherein R_2 has one of the significances given in Table 2, may be prepared

Table 2

Example	R_2	MS/ESI
44		469
45		485
46		470
47		509
48		486
49		547
50		525

Example 51: **{4-[(4-Bromo-phenyl)-phenyl-amino]-4'-methyl-[1,4']bipiperidinyl-1'-yl}-(2,6-dimethyl-phenyl)-methanone**



A mixture of [4-(4-bromo-phenylamino)-4'-methyl-[1,4']bipiperidinyl-1'-yl]-(2,6-dimethyl-phenyl)-methanone (97 mg; 0.20 mmol), Iodobenzene (41 mg; 0.20 mmol), Pd $(OAc)_2$ (1.9 mg; 0.008 mmol), BINAP (5.7 mg; 0.009 mmol) and t-BuOK (0.23 ml of 1 M solution on THF) in toluene (3 ml) is heated at 110°C for 16h. The mixture is diluted with ethyl acetate and filtered. The resulting solution is extracted with 2N NaOH and brine and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (first SiO_2, t-butyl methylether/cyclohexane 1:4→1:0 and subsequently RP-18, methanol/H_2O 7:3). The title compound is isolated as a colorless solid. MS/ESI 560 $(M+H)^+$.

[4-(4-bromo-pherylamino)-4'-methyl-[1,4] bipiperidinyl-1'yl]-2,6-dimethylphenyl)-methanone, used as starting material, may be prepared as follows:

a) 8-(1-Benzyl-4-methyl-piperidin-4-yl)-1,4-dioxa-8-aza-spiro[4.5]decane is prepared from 1,4-dioxa-8-aza-spiro[4.5]decane and 1-benzyl-piperidin-4-one following a procedure as described in example 1c). MS/ESI 331 $(M+H)^+$.

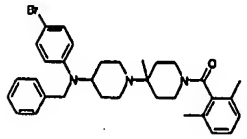
b) A mixture of 8-(1-benzyl-4-methyl-piperidin-4-yl)-1,4-dioxa-8-aza-spiro[4.5]decane (2.0 g, 6.1 mmol) and $Pd(OH)_2$ (20%) on charcoal (1 g) in methanol (30 ml) is hydrogenated for 16h at RT. The catalyst is filtered off and the solvent removed. Crude 8-(4-methyl-piperidin-4-yl)-1,4-dioxa-8-aza-spiro[4.5]decane is isolated as a yellow oil. MS/ESI 241 $(M+H)^+$.

c) (2,6-Dimethyl-phenyl)-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-4-methyl-piperidin-1-yl]-methanone is obtained from crude 8-(4-methyl-piperidin-4-yl)-1,4-dioxa-8-aza-spiro[4.5]decane and 2,6-dimethyl-benzoic acid by following a procedure as described in example 1. MS/ESI 373 $(M+H)^+$.

d) A solution of (2,6-dimethyl-phenyl)-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)-4-methyl-piperidin-1-yl]-methanone (915 mg; 2.46 mmol) in dioxan (30 ml) and HCl (6N; 30ml) is stirred for 4h at 50°C. The mixture is diluted with ethyl acetate (50 ml), extracted with 2N NaOH and brine and dried with sodium sulfate. Removal of the solvent affords 1'-(2,6-dimethyl-benzoyl)-4'-methyl-[1,4']bipiperidinyl-4-one is isolated as a colorless solid. MS/ESI 329 $(M+H)^+$.

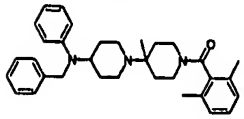
e) A mixture of 1'-(2,6-dimethyl-benzoyl)-4'-methyl-[1,4']bipiperidinyl-4-one (49.3 mg; 0.15 mmol), 4-bromo-phenylamine (29 mg, 0.165 mmol), acetic acid (18 mg; 0.30 mmol) and $NaBH(OAc)_3$ (35 mg; 0.165 mmol) in $(CH_2Cl)_2$ (4 ml) is stirred for 16h at RT. The mixture is diluted with ethyl acetate, extracted with 2N NaOH and brine and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (RP-18, methanol/H_2O 8:2→1:0). [4-(4-bromo-pherylamino)-4'-methyl-[1,4] bipiperidinyl-1'yl]-2,6-dimethylphenyl)-methanone is isolated as a colorless solid. MS/ESI 484 $(M+H)^+$.

Example 52: **{4-[Benzyl-(4-bromo-phenyl)-amino]-4'-methyl-[1,4']bipiperidinyl-1'-yl}-(2,6-dimethyl-phenyl)-methanone**



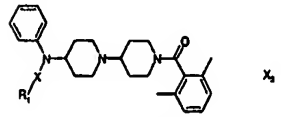
A mixture of {4-[(4-bromo-phenyl)-phenyl-amino]-4'-methyl-[1,4']bipiperidinyl-1'-yl}-(2,6-dimethyl-phenyl)-methanone (97 mg; 0.20 mmol), bromomethyl-benzene (376 mg, 2.2 mmol) and K_2CO_3 (138 mg; 1.0 mmol) in DMF (3 ml) is stirred at 100°C for 16h. The mixture is diluted with ethyl acetate, extracted with 2N NaOH and brine and dried with sodium sulfate. The solvent is removed and the residue subjected to chromatography (first SiO_2, t-butyl methylether and subsequently RP-18, methanol/H_2O 8:2). The title compound is isolated as a colorless solid. MS/ESI 574 $(M+H)^+$.

Example 53: **[4-(Benzyl-phenyl-amino)-4'-methyl-[1,4']bipiperidinyl-1'-yl]-(2,6-dimethyl-phenyl)-methanone**



It is prepared from (2,6-dimethyl-phenyl)-(4'-methyl-4-phenylamino-[1,4']bipiperidinyl-1'-yl)-methanone and benzyl bromide following a similar procedure as described in example 52. MS/ESI 496 $(M+H)^+$. The starting material may be prepared from 1'-(2,6-dimethyl-benzoyl)-4'-methyl-[1,4']bipiperidinyl-4-one, by following a similar procedure as described in example 51e). MS/ESI 406 $(M+H)^+$.

By following the procedure of Example 53 above and using the appropriate starting materials the compounds of formula X_3

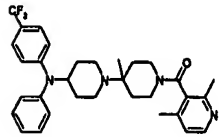


wherein -X-R_1 has the significances as indicated in Table 3 below, may be prepared.

Table 3

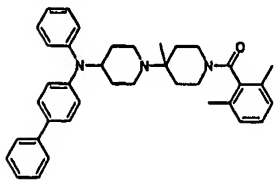
Example	-X-R_1	MS/ESI $(M+H)^+$
54		517
55		497

Example 56: **(2,4-Dimethyl-pyridin-3-yl)-{4'-methyl-4-[phenyl-(4-trifluoromethyl-phenyl)-amino]-[1,4']bipiperidinyl-1'-yl]-methanone**



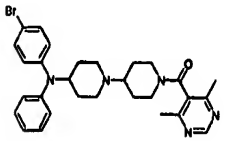
It is prepared from 4-(4-trifluoromethyl-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester by using a procedure as described in example 1. MS/ESI 551 $(M+H)^+$. The starting material is prepared from 4-trifluoromethyl-phenylamine and 4-oxo-piperidine-1-carboxylic acid tert-butyl ester following a procedure as described in example 51e). MS/ESI 345 $(M+H)^+$.

Example 57: **[4-(Biphenyl-4-yl-phenyl-amino)-4'-methyl-[1,4']bipiperidinyl-1'-yl]-(2,6-dimethyl-phenyl)-methanone**



It is prepared from 4-phenylamino-piperidine-1-carboxylic acid tert-butyl ester and 4-bromo-biphenyl by using a procedure as described in example 1. MS/ESI 558 $(M+H)^+$.

Example 58: **{4-[(4-Bromo-phenyl)-phenyl-amino]-[1,4']bipiperidinyl-1'-yl}-(4,6-dimethyl-pyrimidin-5-yl)-methanone**



It is prepared from [1,4']bipiperidinyl-4-yl-(4-bromo-phenyl)-phenyl-amine and 4,6-dimethyl-pyrimidine-5-carboxylic acid by following a procedure as described in example 1. MS/ESI 548 $(M+H)^+$.

[1,4']bipiperidinyl-4-yl-(4-bromo-phenyl)-phenyl-amine used as starting materials may be prepared as follows:

a) 4-(4-Bromo-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester is prepared from 4-bromo-phenylamine and 4-oxo-piperidine-1-carboxylic acid tert-butyl ester as described in example 51e). MS/ESI 355 $(M+H)^+$.

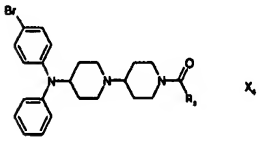
b) 4-[(4-Bromo-phenyl)-phenyl-amino]-piperidine-1-carboxylic acid tert-butyl ester is prepared from 4-(4-bromo-phenylamino)-piperidine-1-carboxylic acid tert-butyl ester and iodo-benzene as described in example 51. MS/ESI 431 $(M+H)^+$.

c) (4-Bromo-phenyl)-phenyl-piperidin-4-yl-amine is prepared from 4-[(4-bromo-phenyl)-phenyl-amino]-piperidine-1-carboxylic acid tert-butyl ester as described in example 1b). MS/ESI 331 $(M+H)^+$.

d) 4-[(4-Bromo-phenyl)-phenyl-amino]-[1,4']bipiperidinyl-1'-carboxylic acid tert-butyl ester is prepared from (4-bromo-phenyl)-phenyl-piperidin-4-yl-amine and 4-oxo-piperidine-1-carboxylic acid tert-butyl ester as described in example 43a). MS/ESI 514 $(M+H)^+$.

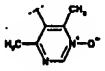
e) [1,4']Bipiperidinyl-4-yl-(4-bromo-phenyl)-phenyl-amine is prepared from 4-[(4-bromo-phenyl)-phenyl-amino]-[1,4']bipiperidinyl-1'-carboxylic acid tert-butyl ester as described in example 1b). MS/ESI 414 $(M+H)^+$.

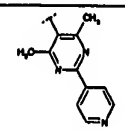
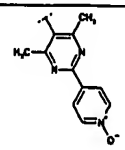
By using a procedure as disclosed above and the corresponding starting materials, the compounds of formula X_4



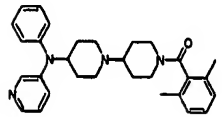
wherein R_2 is as defined in Table 4 below, may be prepared.

Table 4

Example	R_2	MS/ESI $(M+H)^+$
59		546
60		587
61		603
62		563
63		564
64		548

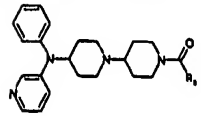
65		625
66		641

Example 67: **(2,6-Dimethyl-phenyl)-[4-(phenyl-pyridin-3-yl-amino)-[1,4']bipiperidinyl-1'-yl]-methanone**



It is prepared from 4-phenylamino-piperidine-1-carboxylic acid tert-butyl ester and 3-bromo-pyridine by using a procedure as described in example 58 and 58b) to e). MS/ESI 469 $(M+H)^+$.

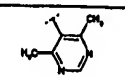
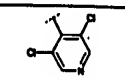
By following a procedure as disclosed above, the compounds of formula X_5

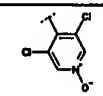
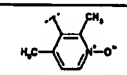
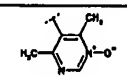


X_5

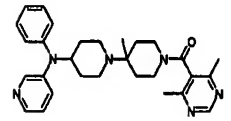
wherein R_2 is as given in Table 5 below, may be prepared.

Table 5

Example	R_2	MS/ESI $(M+H)^+$
68		471
69		510

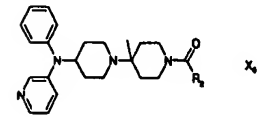
70		526
71		486
72		487

Example 73: **(4,6-Dimethyl-pyrimidin-5-yl)-[4'-methyl-4-(phenyl-pyridin-3-yl-amino)-[1,4']bipiperidinyl-1'-yl]-methanone**



It is prepared from phenyl-piperidin-4-yl-pyridin-3-yl-amine and 4-phenylamino-piperidine-1-carboxylic acid tert-butyl ester using a procedure as described in example 1, 1c) and 1d). MS/ESI 485 $(M+H)^+$.

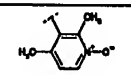
By following the procedure as disclosed in example 73, the compounds of formula X_6



X_6

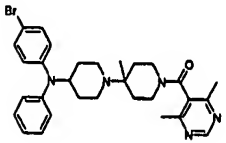
wherein R_2 has the significances as indicated in Table 6, may be prepared.

Table 6

Example	R_2	MS/ESI $(M+H)^+$
74		500

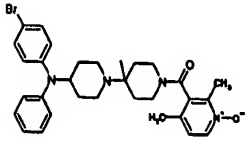
75		540
76		483

Example 77: **{4-[(4-Bromo-phenyl)-phenyl-amino]-4'-methyl-[1,4']bipiperidinyl-1'-yl}-(4,6-dimethyl-pyrimidin-5-yl)-methanone**



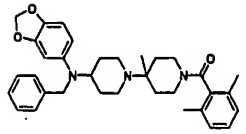
It is prepared from 4-bromo-phenyl)-phenyl-piperidin-4-yl-amine and 4-phenylamino-piperidine-1-carboxylic acid tert-butyl ester using a procedure as described in example 1, 1c) and 1d). MS/ESI 562 $(M+H)^+$.

Example 78: **{4-[4-Bromo-phenyl)-phenyl-amino]-4'-methyl-[1,4']bipiperidinyl-1'-yl}-(2,4-dimethyl-1-oxy-pyridin-3-yl)-methanone**



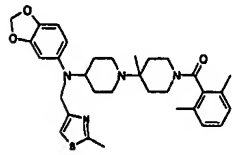
It is prepared from (4-bromo-phenyl)-phenyl-piperidin-4-yl-amine and 4-phenylamino-piperidine-1-carboxylic tert.-butyl ester using a procedure as described in example 1, 1c) and 1d). MS/ESI 577 $(M+H)^+$

Example 79: **[4-(Benzo[1,3]dioxol-5-yl-benzyl-amino)-4'-methyl-[1,4']bipiperidinyl-1'-yl]-(2,6-dimethyl-phenyl)-methanone**



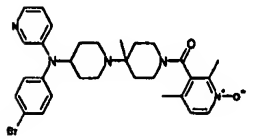
It is prepared from 1'-(2,6-dimethyl-benzoyl)-4'-methyl-[1,4']bipiperidinyl-4-one and benzo[1,3]dioxol-5-ylamine by following a procedure as described in examples 51 and 52. MS/ESI 540 $(M+H)^+$.

Example 80: **{4-[1,3-Benzodioxol-5-yl-(2-methyl-thiazol-4-ylmethyl)-amino]-4'-methyl-1,4'-bipiperidinyl-1'-yl}-(2,6-dimethyl-phenyl)-methanone**



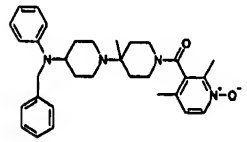
It is prepared from 1'-(2,6-dimethyl-benzoyl)-4'-methyl-[1,4']bipiperidinyl-4-one and benzo[1,3]dioxol-5-ylamine by following a procedure as described in examples 51 and 52. MS(ESI) 561 $(M+H)^+$

Example 81: **{4-[(4-Bromo-phenyl)-pyridin-3-yl-amino]-4'-methyl-[1,4']bipiperidinyl-1'-yl}-(2,4-dimethyl-1-oxy-pyridin-3-yl)-methanone**



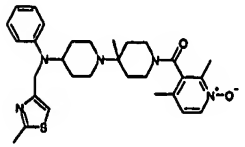
It is prepared from 4-(pyridin-3-ylamino)-piperidine-1-carboxylic acid tert-butyl ester and 1,4-dibromo-benzene by following a procedure as described in example 1. MS/ESI 578 $(M+H)^+$.

Example 82: **[4-(Benzyl-phenyl-amino)-4'-methyl-[1,4']bipiperidinyl-1'-yl]-(2,4-dimethyl-1-oxy-pyridin-3-yl)-methanone**



It is prepared from phenyl-piperidin-4-yl-amine by following a procedure as described in examples 52 and 1. MS/ESI 513 $(M+H)^+$.

Example 83: **(2,4-Dimethyl-1-oxy-pyridin-3-yl)-[4'-methyl-4-[(2-methyl-thiazol-4-ylmethyl)-phenyl-amino]-[1,4']bipiperidinyl-1'-yl]-methanone**



It prepared from (4'-methyl-[1,4']bipiperidinyl-4-yl)-(2-methyl-thiazol-4-ylmethyl)-phenyl-amine using a procedure as described in example 1. MS/ESI 534 $(M+H)^+$.

(4'-methyl-[1,4']bipiperidinyl-4-yl)- (2-methyl-thiazol-4-ylmethyl)-phenyl-amine, used as starting material, is obtained as follows: a mixture of 4-(benzyl-phenylamino)-4'-methyl-[1,4']bipiperidinyl-1'-carboxylic acid tert.-butyl ester (1.0 g, 2.16 mmol), ammonium formate (0.5 g, 7.92 mmol) and $Pd(OH)_2$ (20%) on charcoal (0.25 g) in methanol (25 ml) is heated under reflux for 3 h. The catalyst is filtered off and washed with methanol. The solvent is removed and the residue dissolved in ethyl acetate. The organic solution is extracted with 1N NaOH and brine and dried with sodium sulfate. Removal of the solvent gives crude 4'-methyl-4-phenylamino-[1,4']bipiperidinyl-1'-carboxylic acid tert.-butyl ester which is used in the next step without further purification. MS/ESI 374 $(M+H)^+$.

4'-Methyl-4-phenylamino-[1,4']bipiperidinyl-1'-carboxylic acid tert.-butyl ester is converted into (4'-methyl-[1,4']bipiperidinyl-4-yl)- (2-methyl-thiazol-4-ylmethyl)-phenyl-amine using a procedure as described in examples 52 and 1d).

The compounds of formula I in free form or in pharmaceutically acceptable salt form exhibit valuable pharmacological properties, e.g. as CCR5 antagonists, e.g. as indicated in in vitro tests and therefore indicated for therapy.

a) CCR5 membrane binding assay

Human CCR5 is used to generate stable transfectants in CHO K1 cells. Membranes prepared from these CCR5 transfectants are used in a radioligand binding assay using 125-I MIP-1α as a ligand and the compounds of formula I are tested for inhibitory activity. The data are reported as IC_{50}, i.e. the concentration of compound required to achieve 50% inhibition of [I-125]MIP-1α binding. In this assay, compounds of formula I have an $IC_{50} \leq 1\mu M$. Compounds of Examples 16, 53 and 83 have an IC_{50} of 2 to 3 nM, respectively.

b) CCR5 functional assay – Ca^{2+} mobilization

Human CCR5 is used to generate stable transfectants in CHO K1 cells. These CCR5 transfectants are used for assessing Ca^{2+} mobilization in response to stimulation by the CCR5 ligands MIP-1α, MIP-1β, HCC-1(9-74) or RANTES. For the assay the cells are loaded with a Ca^{2+}-sensitive fluorochrome (Fluo3 or Fluo4). Ligand concentrations between 0.01 - 100 nM are used to induce Ca^{2+} mobilization which is monitored in a fluorometer with appropriate settings.

To assess the activity of the compounds to be tested, a baseline fluorescence reading is taken after which the compounds at the desired concentration are added to the cells and fluorescence is further recorded for a certain time to assess whether compounds show agonistic effects. Next the agonist is added to the mixture and fluorescence monitored. The inhibition of Ca^{2+} flux in the presence of the compounds to be tested is calculated from the inhibition of maximal fluorescence induced by the agonist. IC_{50} values are calculated from dose-response curves obtained with the compounds. In this assay, compounds of formula I have an $IC_{50} \leq 1\mu M$. For example, compounds of Example 1, 18 and 52 have an IC_{50} of 10, 9 and 4, respectively.

c) CCR5 functional assay – chemotaxis

CCR5 transfectants are generated in Jurkat T cells or the mouse pre B cell line L1.2. Migration of CCR5 transfectants is tested in transwell tissue chamber inserts system with the CCR5 agonist MIP-1α at concentrations of 1-100 nM. Cells migrated in response to the agonist compared to a buffer control are quantified in a flow cytometer. The compounds to be tested are added to the cells and the agonist compartments. IC_{50} values are calculated

from concentration-response curves obtained with the compounds in the presence of MIP-1α. In this assay, compounds of formula I have an $IC_{50} \leq 1\mu M$.

d) Experiments performed in murine animal models show that vessel wall remodeling after experimental injury (e.g. induced by allotransplantation) is significantly inhibited in the absence of functional CCR5.

The compounds of formula I are, therefore, useful in the prevention and/or treatment of diseases or disorders mediated by interactions between chemokine receptors, e.g. CCR5, and their ligands, e.g. in transplantation, such as acute or chronic rejection of organ, tissue or cell allo- or xenografts or delayed graft function, autoimmune diseases, e.g. rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroidis, multiple sclerosis, myasthenia gravis, diabetes type I or II and the disorders associated therewith, vasculitis, pernicious anemia, Sjoegren syndrome, uveitis, psoriasis, alopecia areata and others, allergic diseases, e.g. allergic asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, allergic contact dermatitis, inflammatory diseases optionally with underlying aberrant reactions, e.g. inflammatory bowel disease, Crohn's disease or ulcerative colitis, intrinsic asthma, inflammatory lung injury, inflammatory liver injury, inflammatory glomerular injury, atherosclerosis, osteoarthritis, irritant contact dermatitis and further eczematous dermatitises, seborrhoeic dermatitis, cutaneous manifestations of immunologically-mediated disorders, inflammatory eye disease, keratoconjunctivitis, myocarditis or hepatitis, ischemia/reperfusion injury, e.g. myocardial infarction, stroke, gut ischemia, renal failure or hemorrhage shock, traumatic shock and others, cancer, e.g. solid tumors or lymphatic cancer such as T cell lymphomas or T cell leukemias, metastasizing or angiogenesis, infectious diseases, e.g. toxic shock (e.g. superantigen induced), septic shock, adult respiratory distress syndrome or viral infections, e.g. AIDS. By transplantation is meant allo- or xeno grafts of e.g. cells, tissues or solid organs, for example pancreatic islets, stem cells, bone marrow, corneal tissue, neuronal tissue, heart, lung, combined heart-lung, kidney, liver, bowel, pabcreas, trachea or oesophagus. Chronic rejection is also named graft vessel diseases.

For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.01 to10 mg/kg per body weight. An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5 mg to about 1000 mg, conveniently administered,

for example, in divided doses up to four times a day or in retard form. Suitable unit dosage forms for oral administration comprise from ca. 1 to 500 mg active ingredient.

The compounds of formula I may be administered by any conventional route, in particular enterally, e.g. orally, e.g. in the form of tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Pharmaceutical compositions comprising a compound of formula I in free form or in pharmaceutically acceptable salt form in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent.

The compounds of formula I may be administered in free form or in pharmaceutically acceptable salt form e.g. as indicated above. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

In accordance with the foregoing the present invention further provides:

1.1 A method for preventing or treating disorders or diseases mediated by interactions between chemokine receptors and their ligands, e.g. such as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;

1.2 A method for preventing or treating acute or chronic transplant rejection or inflammatory or autoimmune diseases, e.g. as indicated above, in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof;

2. A compound of formula I or a pharmaceutically acceptable salt thereof for use as a pharmaceutical, e.g. in any of the methods as indicated under 1.1 or 1.2 above.

3. A pharmaceutical composition, e.g. for use in any of the methods as in 1.1 or 1.2 above comprising a compound of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent or carrier therefor.

4. A compound of formula I or a pharmaceutically acceptable salt thereof for use in the preparation of a pharmaceutical composition for use in any of the method as in 1.1 or 1.2 above.

The compounds of formula I may be administered as the sole active ingredient or in conjunction with, e.g. as an adjuvant to, other drugs e.g. in immunosuppressive or immunomodulating regimens or other anti-inflammatory agents, e.g. for the treatment or prevention of allo- or xenograft acute or chronic rejection or inflammatory or autoimmune disorders, a chemotherapeutic agent or an anti-infective agent, e.g. an anti-viral agent such as e.g. an anti-retroviral agent or an antibiotic. For example, the compounds of formula I may be used in combination with a calcineurin inhibitor, e.g. cyclosporin A or FK 506; a macrocyclic lactone having immunosuppressive properties, e.g. rapamycin, 40-O-(2-hydroxyethyl)-rapamycin, CCI779 or ABT578; an ascomycin having immunosuppressive properties, e.g. ABT-281, ASM981, etc.; corticosteroids; cyclophosphamide; azathioprine; methotrexate; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine or an immunosuppressive homologue, analogue or derivative thereof; an accelerating lymphocyte homing agent, e.g. FTY720; monoclonal antibodies to leukocyte receptors, e.g., MHC, CD2, CD3, CD4, CD7, CD8, CD11a/CD18, CD25, CD27, CD28, CD40. CD45, CD58, CD80, CD86, CD137, ICOS, CD150 (SLAM), OX40, 4-1BB or to their ligands, e.g. CD154, or antagonists thereof; other immunomodulatory compounds, e.g. a recombinant binding molecule having at least a portion of the extracellular domain of CTLA4 or a mutant thereof, e.g. an at least extracellular portion of CTLA4 or a mutant thereof joined to a non-CTLA4 protein sequence, e.g. CTLA4Ig (for ex. designated ATCC 68629) or a mutant thereof, e.g. LEA29Y ; adhesion molecule inhibitors, e.g. LFA-1 antagonists, ICAM-1 or -3 antagonists, VCAM-4 antagonists or VLA-4 antagonists; or antichemokine antibodies or antichemokine receptor antibodies or low molecular weight chemokine receptor antagonists, e.g. anti MCP-1 antibodies.

Where the compounds of formula I are administered in conjunction with other immunosuppressive / immunomodulatory, anti-inflammatory or chemotherapeutic therapy, dosages of the co-administered immunosuppressant, immunomodulatory, anti-inflammatory or chemotherapeutic compound will of course vary depending on the type of co-drug employed, e.g. whether it is a steroid or a calcineurin inhibitor, on the specific drug employed, on the condition being treated and so forth. In accordance with the foregoing the present invention provides in a yet further aspect:

5. A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective non-toxic amount of a compound of formula I and at least a second drug substance, e.g. an immunosuppressant,

immunomodulatory, anti-inflammatory, anti-infective or chemotherapeutic drug, e.g. as indicated above.

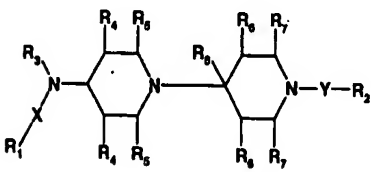
6. A pharmaceutical combination, e.g. a kit, comprising a) a first agent which is a CCR5 antagonist, e.g. a compound of formula I as disclosed herein, in free form or in pharmaceutically acceptable salt form, and b) at least one co-agent, e.g. an immunosuppressant, immunomodulatory, anti-inflammatory, anti-infective or chemotherapeutic drug. The kit may comprise instructions for its administration.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time.

The term "pharmaceutical combination" as used herein means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g. a compound of formula I and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g. a compound of formula I and a co-agent, are both administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

Claims

1. A compound of formula I



I

wherein

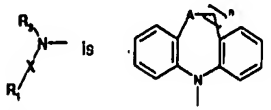
X is a direct bond; $-CH_2-$; $-CH_2-CH_2-$; $-CHR_9-$; -C(O)-; -O-; -NH- or NR_9;

R_1 is optionally R_{10} and/or R_{11}-substituted phenyl; optionally R_{10} and/or R_{11}-substituted heteroaryl; optionally R_{10} and/or R_{11}-substituted heteroaryl N-oxide; or optionally R_{10} and/or R_{11}-substituted naphthyl;

R_2 has one of the significances given for R_1; or is optionally R_{10} and/or R_{11}-substituted fluorenyl; optionally R_{10}-substituted C_1-C_6 alkyl; optionally R_{10}-substituted C_2-C_6 alkenyl; optionally R_{10}-substituted C_3-C_6 cycloalkyl; optionally R_{10}-substituted adamantyl; or optionally R_{10}-substituted C_4-C_6 cycloalkenyl;

R_3 has one of the significances given for R_1; or is optionally R_{10} and/or R_{11}-substituted fluorenyl; R_{10}-substituted C_1-C_6 alkyl; optionally R_{10}-substituted C_2-C_6 alkenyl; optionally R_{10}-substituted C_3-C_6 cycloalkyl; optionally R_{10}-substituted adamantyl; or optionally R_{10}-substituted C_4-C_6 cycloalkenyl;

or



wherein A is $-CH_2-$, -NH-, $-NR_9-$, -S-, -SO-, SO_2- or -O-, n is 0, 1 or 2, and the aromatic rings are each, independently optionally R_{10}-substituted;

each of R4, independently, has one of the significances of R_5; or is CN; OH; OR_9; F; Cl; Br; or I;

each of R_6, independently, is H; C_1-C_6 alkyl; C_1-C_6 hydroxyalkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; phenyl; benzyl; or heteroaryl;

each of R_6, independently, has one of the significances given for R_4;

each of R_7, independently, has one of the significances given for R_5;

R_9 is H; C_1-C_6 alkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl; benzyl; CN; CH_2NH_2; CH_2NHR_9; $CH_2NR_9R_9$; $CH_2NHC(O)R_9$; $CH_2NR_9C(O)R_9$; $CH_2NHC(O)NHR_9$; $CH_2NR_9C(O)NHR_9$; $CH_2NR_9C(O)NR_9R_9$; $CH_2NHC(O)OR_9$; $CH_2NR_9C(O)OR_9$; $CH_2NHSO_2R_9$; $CH_2N(SO_2R_9)_2$; or $CH_2NR_9SO_2R_9$;

each R_9, independently, is C_1-C_6 alkyl; C_3-C_6 cycloalkyl; C_2-C_6 alkenyl; C_2-C_6 alkynyl; phenyl; benzyl; heteroaryl; or CF_3;

R_{10} represents 1 to 4 substituents independently selected from C_1-C_6 alkyl; C_1-C_6 hydroxyalkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; C_3-C_6 cycloalkyl; C_2-C_6 alkenyl; C_3-C_6 cycloalkenyl; C_2-C_6 alkynyl; phenyl; heteroaryl; heteroaryl N-oxide ; F; Cl; Br; I; OH; OR_9; $CONH_2$; $CONHR_9$; $CONR_9R_9$;$OC(O)R_9$; $OC(O)OR_9$; $OC(O)NHR_9$; $OC(O)NR_9R_9$; OSO_2R_9; COOH; $COOR_9$; CF_3; CHF_2; CH_2F; CN; NO_2; NH_2; NHR_9; NR_9R_9; $NHC(O)R_9$; $NR_9C(O)R_9$; $NHC(O)NHR_9$; $NHC(O)NH_2$; $NR_9C(O)NHR_9$; $NR_9C(O)NR_9R_9$; $NHC(O)OR_9$; $NR_9C(O)OR_9$; $NHSO_2R_9$; $N(SO_2R_9)_2$; $NR_9SO_2R_9$; SR_9; $S(O)R_9$; SO_2R_9; $Si(CH_3)_3$ and $B(OC(CH_3)_2)_2$;

R_{11} represents two adjacent substituents which form an annulated 4-7 membered nonaromatic ring optionally containing up to two heteroatoms selected independently from N, O and S; and

Y is a direct bond; -C(O)-; $-C(O)CH_2-$; -S(O)-; $-S(O_2)-$; -C(S)-; $-CH_2-$; $-C(-CH_2-CH_2-)-$; $-CH(R_5)-$ or $-C(R_4)_2-$,

in free form or in salt form.

2. A compound according to claim 1, wherein R_1 is phenyl or heteroaryl, each being optionally substituted by R_{10}; or phenyl optionally substituted by R_{11}; wherein R_{10} represents 1 to 3 substituents independently selected from C_1-C_6 alkyl; C_1-C_6 hydroxyalkyl; C_2-C_6 alkoxyalkyl; C_1-C_6 halogenoalkyl; C_3-C_6 cycloalkyl; C_2-C_6 alkenyl; C_3-C_6 cycloalkenyl; C_2-C_6 alkynyl; phenyl; heteroaryl; heteroaryl N-oxide; F; Cl; Br; I; OH; OR_9; $CONH_2$; $CONHR_9$; $CONR_9R_9$; $OC(O)R_9$; $OC(O)OR_9$; $OC(O)NHR_9$; $OC(O)NR_9R_9$; OSO_2R_9; COOH; $COOR_9$; CF_3; CHF_2; CH_2F; CN; NO_2; NH_2; NHR_9; NR_9R_9; $NHC(O)R_9$; $NR_9C(O)R_9$; $NHC(O)NHR_9$; $NHC(O)NH_2$; $NR_9C(O)NHR_9$; $NR_9C(O)NR_9R_9$; $NHC(O)OR_9$; $NR_9C(O)OR_9$; $NHSO_2R_9$; $N(SO_2R_9)_2$; $NR_9SO_2R_9$; SR_9; $S(O)R_9$; SO_2R_9 and $Si(CH_3)_3$ and R_{11} is an annulated 5 or 6 membered non aromatic ring optionally containing 1 or 2 oxygen atoms, and attached to 2 adjacent carbon atoms.

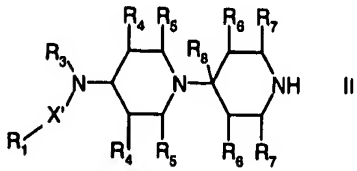
3. A compound according to claim 1, wherein each of R_4, R_5, R_6 or R_7 independently, is H; C_{1-6} alkyl; or benzyl.

4. A compound according to claim 1, wherein R_8 is H; C_{1-6} alkyl; or C_{2-6} alkenyl.

5. A compound according to claim 1 wherein X is a direct bond or $-CH_2-$ and / or Y is –C(O)-.

6. A process for the preparation of a compound of formula I according to claim 1, which process comprises

a) for the preparation of a compound of formula I wherein X is a direct bond, $-CH_2-$, $-CH_2-CH_2-$ or $-CHR_9-$ and Y is -CO-, $-C(O)CH_2-$, -S(O)- or $-S(O_2)-$, amidating a compound of formula II



II

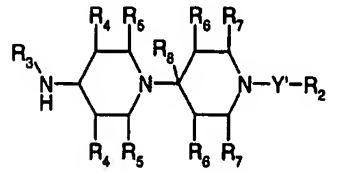
wherein R_1 and R_3 to R_8 are as indicated above and X' is a direct bond, $-CH_2-$, $-CH_2-CH_2-$ or $-CHR_9-$
with a compound of formula III

$$R_2\text{-}Y'\text{-}A' \qquad III$$

wherein R_2 is as defined above, Y' is -CO-, $-C(O)CH_2-$, -S(O)- or $-S(O_2)-$ and A' is a leaving group, e.g. Cl, Br or OH,

b) for the preparation of a compound of formula I wherein X is a direct bond and Y is $-CH_2-$, submitting a compound of formula II as defined above wherein X' is a direct bond, to a reductive amination; or

c) for the preparation of a compound of formula I wherein X is CH_2-, $-CH_2-CH_2-$ or $-CHR_9-$ and Y is -CO-, $-C(O)CH_2-$, -S(O)- or $-S(O_2)-$, reacting a compound of formula IV



IV

wherein R_2 to R_8 and Y' are as defined above, with a compound of formula V

$$R_1\text{—}X''\text{—}Hal \qquad V$$

wherein R_1 is as defined above and X'' is CH_2- or $-CHR_9-$;

and, where required, converting the resulting compound of formula I obtained in free form into the desired salt form, or vice versa.

7. A compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof for use as a pharmaceutical.

8. A pharmaceutical composition comprising a compound of formula I according to claim 1 or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable diluent a carrier therefor.

9. A pharmaceutical combination comprising

a) a first agent which is a compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof, and

b) at least one co-agent.

10. A method for preventing or treating disorders or diseases mediated by interactions between chemokine receptors and their ligands, in a subject in need of such a treatment, which method comprises administering to said subject an effective amount of a compound of formula I according to claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/EP 02/03871

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/58 C07D401/14 C07D211/96 C07D417/14 A61K31/4468

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 66559 A (MCCOMBIE STUART W ;CLADER JOHN W (US); SCHERING CORP (US); JOSIEN) 9 November 2000 (2000-11-09) page 1, line 10 -page 2, line 22 claim 1 ---	1-10
X	DE 196 43 331 A (THOMAE GMBH DR K) 23 April 1998 (1998-04-23) claim 1 ---	1-4
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	-/--	

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 August 2002	23/08/2002
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Fanni, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In tional Application No
PCT/EP 02/03871

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	WO 02 22592 A (SCHERING CORP) 21 March 2002 (2002-03-21) page 79; examples 286,287 claim 1 ---	1
A	WO 98 11128 A (EBERLEIN WOLFGANG ;ENTZEROTH MICHAEL (DE); HALLERMAYER GERHARD (DE) 19 March 1998 (1998-03-19) page 125; examples 565,566 claim 1 page 127; claims 584,587,588 ---	1
A	WO 98 11082 A (DIMOUDIS NIKOLAOS ;FRIEBE WALTER GUNAR (DE); MICHAELIS UWE (DE); K) 19 March 1998 (1998-03-19) examples 20,27,32 claim 1 -----	1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

International Application No. PCT/EP 02 03871

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/03871

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/03871

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